Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 8157–8160
Tetrahedron Letters

Ionic liquids incorporating camphorsulfonamide units for the Ti-promoted asymmetric diethylzinc addition to benzaldehyde

Benoît Gadenne, Peter Hesemann and Joël J. E. Moreau*

UMR5076 CNRS/ENSCM, Hétérochimie Moléculaire et Macromoléculaire, 8, rue de l'Ecole Normale, 34296 Montpellier, France

Received 15 July 2004; revised 3 September 2004; accepted 6 September 2004
Available online 21 September 2004

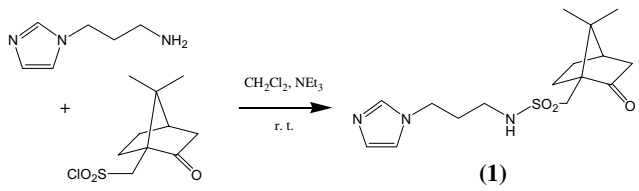
Abstract—New hydrophobic ionic liquids containing chiral camphorsulfonamide units were used as chiral auxiliaries in the titanium catalyzed asymmetric diethylzinc addition to benzaldehyde. The ionic catalyst system shows catalytic properties similar to those of related nonionic counterparts in terms of activity and enantioselectivity. Interestingly, the ionic ligands can easily be recycled and re-used without loss of activity or selectivity.

Transition metal catalysis in ionic liquids (ILs) is a field of intense research activity and led to numerous applications in organic synthesis[1,2] and asymmetric catalysis.[3] A variety of catalytic reactions was successfully performed in biphasic mixtures consisting in ionic liquids and nonpolar organic solvents. This 'heterogenization' of reaction media offers a promising way for catalyst separation and recovery. The utilization of task specific ionic liquids (TSILs) as metal ligands[4] is also attractive in view of the recycling of the ionic auxiliary. This strategy, particularly interesting for precious chiral auxiliaries for asymmetric catalysis, leads also to enhanced catalyst stability and avoids catalyst leaching.[5]

Our current interest in heterogenized enantioselective catalyst systems[6] led us to explore functionalized ionic compounds bearing chiral entities. Here, we report the use of TSILs as reusable chiral auxiliaries in homogeneous asymmetric catalysis using organic solvents as reaction media. We wanted to take advantage of the solubility of numerous hydrophobic ionic liquids in polar organic solvents (dichloromethane, alcohols) in order to perform asymmetric reactions in a monophasic reaction medium. This approach presents several advantages compared with catalytic reactions performed in biphasic reaction media. (1) It avoids the utilization of conventional ionic liquids based on imidazolium species, which may appear of low chemical stability.[7] (2) Diffusion problems can be excluded, as the reactions are performed in monophasic media. (3) Since ionic compounds are insoluble in nonpolar solvents, the pure functional ionic liquid can easily be separated from the reaction products by a simple diethyl ether treatment. The recovered chiral ionic auxiliary can subsequently be re-used for a new reaction cycle.

We decided to focus on the synthesis of ionic compounds bearing chiral camphorsulfonamide units. Yus et al. described that camphorsulfonamides are efficient chiral ligands in the titanium promoted addition of organozinc reagents to aldehydes and ketones.[8] A large variety of chiral ligands bearing camphorsulfonamide units has been studied during the last few years.[9]

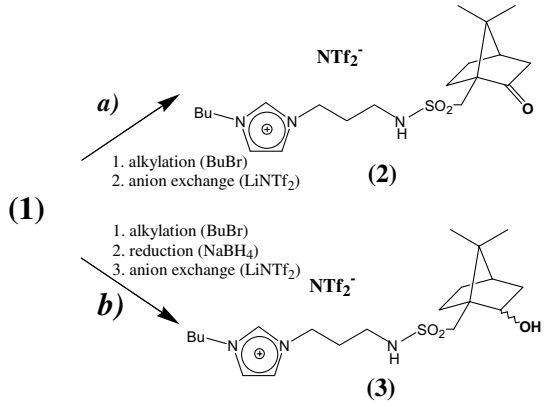
The synthesis of an imidazole functionalized camphorsulfonamide was firstly achieved by reacting D-camphor-10-sulfonyl chloride and *N*-(3-aminopropyl)-imidazole **1** (Scheme 1).



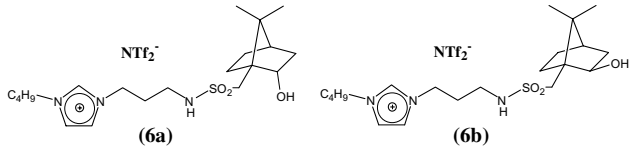
Scheme 1. Synthesis of the imidazole functionalized D-camphorsulfonamide (**1**).

Keywords: Ionic liquids; Asymmetric catalysis; Chiral auxiliaries.
* Corresponding author. Tel.: +33 4 67 14 72 11; fax: +33 4 67 14 72 12; e-mail: jmoreau@cit.enscm.fr

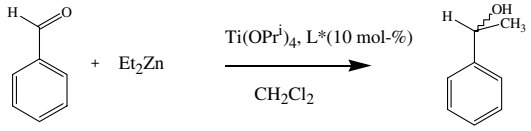
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.09.038



Scheme 2. Synthesis of TSILs bearing camphorsulfonamide entities.



Scheme 4. TSILs bearing borneol (**6a**) and isoborneol (**6b**) entities.



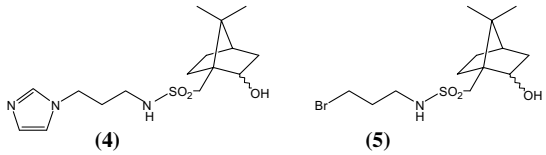
Scheme 5. Addition of diethylzinc to benzaldehyde.

Alkylation of **1** with *n*-butylbromide and subsequent anion exchange using lithio-bis-trifluorosulfonylimide led to the formation of the hydrophobic ionic compound **2** functionalized with D-camphorsulfonamide entities (Scheme 2, ***a***).

In a similar way, we synthesized ionic compounds bearing borneol units. The ionic compound **3** was prepared in a three step synthesis involving an alkylation–reduction–anion exchange sequence from the imidazole functionalized camphorsulfonamide **1** (Scheme 2, ***b***). The reduction of the keto group of the camphor unit in **1** was performed using sodium borohydride, yielding a mixture of ionic borneol (*endo*-) and isoborneol (*exo*-) diastereoisomers. The *exo*:*endo* ratio of the hydroxyl groups in the reduced product, determined by ^{1}H NMR spectroscopy, was found to be 60:40.[8a]

The *exo*/*endo* stereochemistry of the hydroxyl group is of particular importance for the selectivity of the borneol derived ligands. Isoborneol (*exo*-borneol) derivatives showed higher selectivities than the corresponding borneol diastereoisomers.[8a] We therefore synthesized enantiopure samples of these chiral ionic auxiliaries. As the separation of the diastereoisomeric functionalized borneol derivatives **4** by column chromatography was unsuccessful, we synthesized the brominated sulfonamide **5** (Scheme 3) by coupling 3-bromopropylammonium bromide with D-camphor-10-sulfonyl chloride and subsequent reduction using sodium borohydride. Column chromatography allowed the separation of the two diastereoisomers.

Reaction of *exo*-**5** and *endo*-**5** with *n*-butylimidazole, followed by bromide–bis-trifluorosulfonylimide exchange led to the enantiopure ionic liquids functionalized either with borneol (**6a**) or isoborneol groups (**6b**) (Scheme 4).[10]



Scheme 3. Borneol/isoborneol sulfonamides functionalized with imidazole (**4**) and bromide (**5**) groups.

The catalytic properties of the ligands **1**, **2**, **3**, **6a** and **6b** were evaluated in the addition of diethylzinc to benzaldehyde (Scheme 5).[11]

The test reaction was carried out in homogeneous solution using dichloromethane as solvent.[12] The treatment of the reaction mixture by a simple evaporation–hydrolysis–diethyl ether work-up permitted the separation of the chiral ionic liquids from the reaction products. The recovered ionic camphorsulfonamide ligands were reused in other reaction cycles.

The results are summarized in Table 1.

The evaluation of the catalytic properties of the chiral ligands showed high activities for all synthesized chiral auxiliaries. In all cases, the observed conversions in the Ti^{IV}-catalyzed alkylation of benzaldehyde in the presence of the camphorsulfonamide ligands were >99%.

Concerning the enantioselectivity, the nonionic camphorsulfonamide ligand **1** showed low enantioselectivity (3% ee, entry 1), which may be due to a coordinating effect of the terminal imidazole substructures. Increased

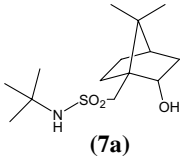
Table 1. Enantioselective addition of diethylzinc to benzaldehyde[a]

Entry	Ligand	ee (configuration)[b]			
		First cycle	Second cycle	Third cycle	Fourth cycle
1	**1**	3 (*S*)	—	—	—
2	**2**	40 (*S*)	39 (*S*)	39 (*S*)	38 (*S*)
3	**3**	50 (*S*)	49 (*S*)	49 (S)	—
4	**6a**	24 (*S*)	—	—	—
5	**6b**	65 (*S*)	64 (*S*)	65 (*S*)	64 (*S*)
6	**7a**[c]	27 (*S*)	—	—	—
7	**7b**[c]	64 (*S*)	—	—	—

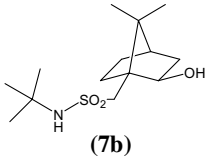
[a] General reaction conditions: benzaldehyde:ligand:Ti(O*i*Pr)$_4$:Et$_2$Zn = 1.0:0.1:1.1:1.2 (molar ratio), reaction time 18 h, reaction temperature 25 °C.
[b] Determined by HPLC using a Daicel Chiralcel OD column.
[c] Ref. 8a.

enantioselectivity is observed with the corresponding alkylated imidazolium compound **2** (40% ee, entry 2).

We also tested three different ionic borneol derived ligands **3**, **6a** and **6b**. The diastereoisomeric mixture **3** containing the *exo*- and *endo*-isomer (ratio: 60:40) gave a slightly higher enantioselectivity than the ionic camphorsulfonamide ligand **2** (50% ee, entry 3). The enantiopure samples **6a** and **6b** led to the formation of (*S*)-1-phenylpropanol with ee values of 24% and 65%, respectively (entries 4 and 5). The ionic ligand appeared efficient since the obtained enantioselectivities are similar to those reported for related nonionic species as for the *tert*-butyl derivatives **7a** and **7b** (entries 6 and 7).[8a]



(7a)



(7b)

We also studied the recycling of the ionic chiral auxiliaries. After the separation from the reaction products, by an ether treatment, the ionic ligands **2**, **3** and **6b** were reused up to three times in the asymmetric addition of diethylzinc to benzaldehyde. We observed no variation of the catalytic activity or selectivity of the ionic compounds (entries 2, 3 and 5). The identical spectroscopic properties of the TSILs after the repeated reaction cycles indicated high chemical stability of the ionic ligands under the reaction conditions.

In conclusion, we report the utilization of new chiral TSILs as enantioselective ligands in homogeneous asymmetric catalysis. Here, we focused on the synthesis of new TSILs functionalized with camphor- and borneol-sulfonamides. These ionic ligands show catalytic properties similar to nonionic counterparts.[8a] This approach offers advantages in combining homogeneous catalysis and easy separation of the chiral ionic ligand. The ionic ligand can be re-used several times without loss in activity or selectivity.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.09.038.

References and notes

1. Wasserscheid, P.; Welton, T. *Ionic Liquids in Synthesis*; Wiley-VCH: Weinheim, 2002.
2. Recent review articles: (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083; (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772–3789; (c) Sheldon, R. *Chem. Commun.* **2001**, 2399–2407; (d) Gordon, C. M. *Appl. Catal. A: General* **2001**, *222*, 101–117.
3. For a review article see: (a) Baudequin, C.; Baudoux, J.; Levillain, J.; Cahard, D.; Gaumont, A.-C.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2003**, *14*, 3081; Asymmetric catalysis in ionic liquids: (b) Song, C. E.; Roh, E. J. *Chem. Commun.* **2000**, 837–838; (c) Guernik, S.; Wolfson, A.; Herskowitz, M.; Greenspoon, N.; Geresh, S. *Chem. Commun.* **2001**, 2314–2315; (d) Yinghuai, Z.; Carpenter, K.; Bun, C. C.; Bahnmueller, S.; Ke, C. P.; Srid, V. S.; Kee, L. W.; Hawthorne, M. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3792–3795; (e) Loh, T. P.; Feng, L. C.; Yang, H. Y.; Yang, J. Y. *Tetrahedron Lett.* **2002**, *43*, 8741; (f) Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Carrié, D.; Vaultier, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1891; (g) Lozano, P.; de Diego, T.; Carrié, D.; Vaultier, M.; Iborra, J. L. *Chem. Commun.* **2002**, 692; (h) Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Gmough, S.; Vaultier, M. *Green Chem.* **2004**, *6*, 93.
4. (a) Audric, N.; Clavier, H.; Mauduit, M.; Guillemin, J.-C. *J. Am. Chem. Soc.* **2003**, *125*, 9248; (b) Yao, Q.; Zhang, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3395; (c) Bronger, R. P. J.; Silva, S. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Chem. Commun.* **2002**, 3044; (d) Wasserscheid, P.; Waffenschmidt, H.; Machnitzki, P.; Kottsieper, K. W.; Stelzer, O. *Chem. Commun.* **2001**, 451; (e) Favre, F.; Olivier-Bourbigou, H.; Commereuc, D.; Saussine, L. *Chem. Commun.* **2001**, 1360; (f) Brasse, C. C.; Englert, U.; Salzer, A. *Organometallics* **2000**, *19*, 3818.
5. Chiral ionic liquids in asymmetric catalysis: (a) Baleizão, C.; Gigante, B.; Garcia, H.; Corma, A. *Tetrahedron Lett.* **2003**, *44*, 6813; (b) Lee, S. G.; Zhang, Y. J.; Piao, J. Y.; Yoon, H.; Song, C. E.; Choi, J. H.; Hong, J. *Chem. Commun.* **2003**, 2624.
6. (a) Hesemann, P.; Moreau, J. J. E. *Tetrahedron: Asymmetry* **2000**, *11*, 2183; (b) Herres, S.; Hesemann, P.; Moreau, J. J. E. *Eur. J. Org. Chem.* **2003**, 99; (c) Brethon, A.; Moreau, J. J. E.; Wong Chi Man, M. *Tetrahedron: Asymmetry* **2004**, *15*, 495.
7. Aggarwal, V. K.; Emme, I.; Mereu, A. *Chem. Commun.* **2002**, 1612.
8. (a) Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2479; (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284, and references cited therein.
9. (a) Bauer, T.; Gajewiak, J. *Tetrahedron* **2003**, *59*, 10009; (b) García, C.; Walsh, P. J. *Org. Lett.* **2003**, *5*, 3641; (c) Jeon, S.-J.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 9544, and references cited therein.
10. Selected data for 1-butyl-3-3-[(1*S*,2*S*,4*S*)-(2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethyl)sulfamoyl]-propyl-3*H*-imidazol-1-ium bis-(trifluoromethanesulfonyl)imide **6a**: ^{1}H NMR ($CDCl_3$): δ 0.8–1.1 (m, 9H, $3\times CH_3$), 1.20–1.40 (m, 3H, CH + CH_2), 1.68–1.95 (m, 4H, $2\times CH_2$), 2.10–2.20 (m, 2H), 2.25–2.4 (m, 2H), 2.98 (d, 1H, J = 14.4 Hz), 3.10 (d, 1H, J = 14.4 Hz), 3.10–3.20 (m, 2H), 3.94 (br s, 1H), 4.00 (t, 2H, J = 7.2 Hz), 4.14 (t, 2H, J = 7.4 Hz), 4.22–4.40 (m, 3H, CH + CH_2), 6.08 (br s, 1H), 7.26 (s, 1H), 7.47 (s, 1H), 8.80 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 19.1, 19.8, 20.7, 24.1, 28.6, 30.5, 32.1, 39.0, 40.3, 44.4, 47.6, 50.4, 51.3, 51.9, 55.2, 75.6, 120.3 (q, $-CF_3$, J = 323 Hz), 122.6, 123.2, 136.1; HRMS [FAB+] calcd. for $C_{20}H_{36}N_3O_3S_1$ $(M)^+$ 398.2477, found 398.2501; $[\alpha]_D^{25}$ +5.5 (*c* 0.55, CH_2Cl_2).Selected data for 1-butyl-3-3-[(1*S*,2*R*,4*S*)- (2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]hept-1-ylmethyl)sulfamoyl]-propyl-3*H*-imidazol-1-ium bis-(trifluoromethanesulfonyl)imide **6b**: ^{1}H NMR ($CDCl_3$): δ 0.78 (s, 3H), 0.92 (t, 3H, J = 7.4 Hz), 1.01 (s, 3H), 1.22–1.46 (m, 3H, CH + CH_2), 1.56–1.89 (m, 8H, $4\times CH_2$), 2.12 (m, 2H), 2.87 (d, 1H, J = 13.9 Hz), 3.15 (m, 3H, CH + CH_2), 3.39 (d, 1H, J = 13.9 Hz), 3.99 (m, 1H), 4.12 (t, 2H, J = 7.4 Hz), 4.31 (t, 2H, J = 6.4 Hz), 5.61 (bt, 1H), 7.27 (s, 1H), 7.44 (s, 1H), 8.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.6, 19.8, 20.1, 20.7, 27.7, 30.4, 30.9, 32.1, 39.5, 40.1,

44.8, 47.4, 49.2, 50.4, 50.7, 51.8, 76.7, 120.1 (q, $-CF_3$, $J = 321$ Hz), 122.7, 123.2, 136.0; HRMS [FAB+] calcd. for $C_{20}H_{36}N_3O_3S_1$ $(M)^+$ 398.2477, found 398.2477; $[\alpha]_D^{25}$ −16.4 (*c* 0.97, CH_2Cl_2).

11. (a) Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739; (b) Pu, L. *Chem. Rev.* **2001**, *101*, 757–824.
12. General procedure for the asymmetric addition of diethylzinc to benzaldehyde. A Schlenk tube equipped with a stirring bar was charged with the ionic liquid (0.25 mmol). After drying in vacuo, the solvent dichloromethane (10 mL) and Ti(O-*i*Pr)$_4$ (810 μL, 2.75 mmol) were added. The resulting mixture was stirred at room temperature for 1 h. Then, diethylzinc (1 M in hexane) (3.0 mL, 3.0 mmol) was added. The resulting homogeneous solution was stirred for another 15 min and benzaldehyde (228 μL, 2.5 mmol) was added. After stirring at room temperature during 18 h, the solvent was pumped off. The reaction mixture was dissolved in 1 mL of EtOH and quenched by the addition of 15 mL of 1 N hydrochloric acid. The diethyl ether extract of this mixture was dried and the conversion and ee value were determined by ^{1}H NMR and chiral HPLC (stationary phase: Chiralcel OD, mobile phase: hexane/isopropanol 9/1), respectively. A second extraction of the hydrolysed reaction medium using dichloromethane afforded the TSIL. The purity of the recovered TSIL was checked by ^{1}H NMR after washing the CH_2Cl_2 extract with 1 N hydrochloric acid and water, drying and solvent evaporation.